

REMARKS

Status of the Claims

Claims 1-11, 16, and 17 are pending and under consideration in this application. Claims 1-4, 8-11, 16, and 17 stand rejected and claims 6 and 7 are objected to. Claims 16 and 17 are cancelled without prejudice to their being presented in a separate application. No new matter has been added.

After entry of the cancellations made herein, claims 1-11 will be pending and under consideration.

Rejections Under 35 U.S.C. § 103(a) (Obviousness)

(1) At pages 4-5, claims 16 and 17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Naughton (U.S. Patent Publication No. 2002/0038152 A1) in view of “applicants admission” or Hubbard et al. (U.S. Patent No. 5,922,025).

According to the Office Action,

it would have been obvious, if not inherent, to one of ordinary skill in the art at the time of the invention to modify the method disclosed by Naughton '152 to include the step of implanting the matrix directly into vocal cord muscle as taught by Applicant's specification or Hubbard in order to increase bulk of the vocal cord to treat vocal cord paralysis.

Although applicants disagree with this characterization, claims 16 and 17 have been cancelled without prejudice thereby rendering their rejection under 35 U.S.C. § 103(a) moot.

(2) At page 3, claims 1-4, 8, 9, and 11 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Boss Jr. (U.S. Patent No. 5,591,444; hereinafter referred to as the “Boss Jr.”) in view of Daniels et al. (U.S. Patent No. 3,949,073; hereinafter referred to as “Daniels et al.”). Applicants respectfully traverse this rejection.

According to the Office Action,

it would have been obvious for one of ordinary skill in the art to modify the method described by Boss Jr by utilizing a phosphate buffered solution to rinse the cells and apply the method to tissue of the vocal cord to

correct vocal cord defects as taught by Daniels et al. in order to treat a vocal cord. (see Office Action, page 5, lines 13-16.)

Applicants respectfully disagree with this characterization.

The MPEP states that to properly establish a *prima facie* case of obviousness, three basic criteria must be met: First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP § 2142 citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 is drawn to a method for corrective surgery in a human subject of a vocal cord defect amenable to rectification by the augmentation of tissue subadjacent to the vocal cord defect, which includes the steps of: placing an effective amount of autologous *in vitro* cultured cells into a vocal cord tissue of the subject in a position subadjacent to the vocal cord defect, wherein the vocal cord tissue is selected from the group consisting of a scar, Reinke's space, a muscle of the vocal cord, and the lamina propria, and wherein the *in vitro* cultured cells are obtained by culturing a plurality of viable cells retrieved from the subject.

Boss Jr. discloses a method of repairing subcutaneous or dermal tissue in a subject. The method involves the preparation of cultured dermal fibroblasts from a specimen obtained from the subject and the injection of the fibroblast preparation, substantially free of immunogenic proteins, to repair the subcutaneous or dermal tissue (see Abstract of Boss Jr.). However, as acknowledged by the Office Action, "Boss Jr. discloses example applications of the method such as depressed scars and wrinkles, but not expressly for vocal cord and furthermore lacks the express disclosure of including a phosphate buffered solution" (see Office Action, page 5, lines 7-9).

In addition, Boss Jr. describes the use of cultured dermal fibroblasts for the treatment of depressed scars and wrinkles as highly preferable to the use of other types of treatments, e.g.,

silicone or collagen. In particular, collagen's (unprocessed bovine collagen, processed or modified bovine collagen (atelocollagen), or human collagen) utility is stated to be hindered by, *inter alia*, host-immune responses (inflammation), absorption by patient, lack of long-term therapeutic benefit, irregular viscosity (lumpiness), tedious preparation methodologies, and patient discomfort (see Boss Jr. at column 1 line 40 through column 3, line 17). Therefore, in reading the disclosure of Boss Jr., applicants respectfully submit that the skilled artisan would not have been motivated to look for references (e.g., Daniels et al.) describing the use of collagen for the treatment of superficial, cosmetic problems, much less for internal surgical procedures to repair vocal cord defects. Indeed, one of ordinary skill in the art would have been dissuaded from looking for such a reference by Boss Jr.'s disparaging characterization of collagen usage.

Applicants respectfully point out that the MPEP states that

where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. MPEP § 2143.01 (II) citing *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991).

Daniels et al. is alleged to cure the aforementioned deficiency of Boss Jr. by disclosing a method of corrective surgery for depressed scars and wrinkles as well as vocal cord defects. However, the method of Daniels et al. uses collagen (i.e., *in vivo* polymerizable collagen). Therefore, given Boss Jr.'s disparaging characterization of collagen, applicants respectfully submit there would have been no motivation for one of ordinary skill in the art to combine the teachings of Daniels et al. with Boss Jr.

Moreover, there is absolutely no mention nor even a suggestion in Daniels et al. that cells (cultured or otherwise) be used for such treatments. Daniels et al. does not disclose or even suggest that particular types of cells, such as the fibroblasts or adipocytes recited in the claims, be used for any treatment, let alone the treatment of a vocal cord defect by placing an effective amount of autologous *in vitro* cultured cells into a vocal cord tissue of the subject in a position subadjacent to the vocal cord defect. Therefore, Daniels et al., like Boss Jr., does not provide motivation to combine its disclosure with that of Boss Jr. In addition, Daniels et al. certainly provides no disclosure or even the slightest suggestion of specific regions of the vocal cord (a

scar, Reinke's space, a muscle of the vocal cord, and the lamina propria) in which the cells are to be placed (e.g., injected).

Thus, for the reasons above, the references neither singly or in combination teach or suggest each and every element of the instant claims nor do either of the cited references contain the requisite motivation to one of ordinary skill in the art to combine their respective disclosures to perform the methods of the instant claims. Since there was no motivation to combine the references, there would also be no reasonable expectation of success. Therefore, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

(3) At pages 5-6 of the Office Action, claims 1, 2, and 5 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Agerup (U.S. Patent No. 5,633,001; hereinafter referred to as "Agerup") or Hubbard (U.S. Patent No. 5,922,025; hereinafter referred to as "Hubbard") in view of Vacanti (U.S. Patent No. 5,041,138; hereinafter referred to as "Vacanti"). Applicants respectfully traverse this rejection.

According to the Office Action,

it would have been obvious to one of ordinary skill in the art to modify the method disclosed by Agerup or Hubbard by culturing the cells in vitro before implantation as taught by Vacanti et al. in order to ensure adequate cell volume and density for the cells to survive in vivo (see Office Action, page 6, lines 5-7).

Applicants respectfully disagree with this characterization.

The standard for establishing a *prima facie* case of obviousness and description of independent claim 1 are set forth *supra*.

(a) Agerup discloses a pseudoplastic polymer carrier (and one or more tissue augmenting substances) for augmentation of tissues that need to be enlarged and methods for tissue augmentation using the same. However, as acknowledged by the Office Action, Agerup "lack[s] the express written disclosure of culturing adipose cells in vitro before injection" (see Office Action, page 6, lines 1-2). Moreover, Agerup does not disclose or even suggest: (i) the use of autologous in vitro cultured cells (e.g., fibroblasts or adipocytes), (ii) the placing of the aforementioned cells into a vocal cord tissue of the subject in a position subadjacent to the vocal

cord defect, or (iii) that the vocal cord tissue be a scar, Reinke's space, a muscle of the vocal cord, or the lamina propria.

At column 1, lines 22-24, Agerup discloses that "Materials used for augmentation of tissues are, for instance, the patients own fat cell cartilage," which applicants maintain is not at all clear for the reasons of record (see, e.g., Amendment and Response received May 8, 2006). However, the Office Action states that "[o]ne of ordinary skill in the art, knowing 'fat cell cartilage' does not exist, would interpret the intended teaching to read 'fat cell, cartilage, or other suitable materials'"(underlining added) (Office Action, page 3, lines 8-9). Applicants respectfully submit it is far from clear that the skilled artisan would interpret the intended teaching to be "fat cell, cartilage, or other suitable materials" in that (i) the generic term used to describe "fat cell cartilage" is "Materials" (column 1, line 22) and (ii) the text immediately following the term "fat cell cartilage," and indeed the majority of the text of the patent, refer only to non-cellular agents. Applicants respectfully submit that one skilled in the art would be more likely to consider the term "fat cell cartilage" to refer to some fat cell component than to cells. Applicants respectfully request that the Examiner provide an explanation for the assertion that "one of ordinary skill in the art...would interpret the intended teaching to read "fat cell, cartilage, or other suitable materials." In addition to these considerations, applicants also point out that the single mention in the patent to the use of cells for tissue augmentation is in one sentence in the Background section that states "Homotransplantation of tissue is a cumbersome and painful procedure that has a too short action" (see Agerup at column 1, lines 40-41). Thus, even if Agerup had disclosed, e.g., the use of autologous *in vitro* cultured cells or the placing (e.g., injection) of the cells in a position subadjacent to a vocal cord defect, which it does not, in the above quoted sentence Agerup strongly teaches away from the use of patient tissue (and thus cells) in methods of tissue augmentation.

The Office Action alleges that Vacanti et al. cures the aforementioned deficiency of Agerup. As an initial matter, Vacanti et al. discloses the use of patient tissue in methods of tissue augmentation but makes no mention of vocal cord treatment at all, let alone specific regions of the vocal cord to be treated. Thus, Vacanti et al. provides no motivation to combine

its disclosure with that of Agerup. Even had there been motivation to combine these references, which there was not, Vacanti et al. does not provide what is missing from Agerup. Vacanti et al. discloses artificial matrices for the growth and implantation of cartilaginous structures and surfaces, e.g., that can be molded into a desired shape such as an ear or nose, or flexible matrices for use at a joint, and implantation methods using the same (see Vacanti et al., Abstract). As indicated above, Vacanti et al. contains no disclosure or even suggestion of methods or compositions useful for vocal cord augmentation, let alone what regions of the vocal cords cells could be administered. Thus, Vacanti et al. does not provide the cure for the above-described deficiencies in the disclosure of Agerup and the combination of Agerup and Vacanti et al. does not disclose or even suggest each and every element of the claim 1. Moreover, applicants respectfully submit there would have been no motivation to combine these two references (see above) and thus no reasonable expectation of success.

(b) Hubbard discloses a permanent, biocompatible ceramic material, not fat cells, for soft tissue augmentation and methods for its use (see Hubbard at column 4, lines 11-13). As acknowledged by the Office Action, Hubbard "lack[s] the express written disclosure of culturing adipose cells in vitro before injection" (see Office Action, page 6, lines 1-2). Moreover, Hubbard does not disclose or even suggest: (i) the use of autologous in vitro cultured cells (e.g., fibroblasts or adipocytes), (ii) the placing of the aforementioned cells into a vocal cord tissue of the subject in a position subadjacent to the vocal cord defect, or (iii) that the vocal cord tissue be a scar, Reinke's space, a muscle of the vocal cord, or the lamina propria as is required by the instant claims. Although Hubbard discloses "the use of autologous fat as an alternative to Teflon® collagen as the implantable material for vocal cord medialization, with a view to its use as an alternative to non-autologous injectable material in vocal cord augmentation," applicants respectfully submit that this in no way recites with particularity autologous *in vitro* cultured cells nor the specific sites within the vocal cord tissue (e.g., a scar, Reinke's space, a muscle of the vocal cord, and the lamina propria) to which autologous *in vitro* cultured cells should be administered (see limitations of claim 1).

The Office Action alleges that Vacanti et al. cures the aforementioned deficiency of Hubbard. However, as discussed above, Vacanti et al. contains no disclosure or even suggestion of methods or compositions useful for vocal cord augmentation, let alone what regions of the vocal cords cells could be administered. Thus, Vacanti et al. does not provide the cure for the above-described deficiencies in the disclosure of Hubbard and the combination of Vacanti et al. and Hubbard does not disclose or even suggest each and every element of claim 1. Moreover, in view of the above-described deficiencies in the disclosure of Hubbard and since Vacanti et al. does not disclose or suggest using in vitro cultured cells to treat a vocal cord defect, and certainly not specific regions of the vocal cord where the cells are placed, there would have been no motivation to combine these two references nor a reasonable expectation of success.

In view of the foregoing, applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

(3) Claim 10 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Boss et al. (see above) in view of Daniels et al. (see above), and in further view of Osbourne et al. (U.S. Application Publication No. 2004/015833; hereinafter referred to as "Osbourne et al.").

According to the Office Action, "it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method disclosed by Boss Jr., as modified by Daniels et al., to include culturing the cells in the patient's own serum before implantation to ensure biocompatibility of the implanted cells" (see Office Action at page 6, lines 16-19).

Applicants respectfully disagree with this characterization.

In light of the comments above, the combined teachings of the Boss Jr. and Daniels et al. do not render obvious instant claim 1. Claim 10, dependent on claim 1, adds a further limitation that the patient's own serum be used for culturing the autologous in vitro cultured cells. Insofar as claim 10 depends from a nonobvious claim, it also is not rendered obvious by these two references. Osbourne et al. fails to remedy the deficiencies of the combination of Boss Jr. and Daniels et al. as previously discussed. Osbourne et al. discloses methods of grafting vascular smooth muscle cells that have been transduced with a gene of interest, but contains no mention at

all or even a suggestion of vocal cords, nor regions of vocal cords to which cells could be administered. Thus, in that the combination of cited references do not disclose or even suggest each and every element of claim 1, claim 1 (and claim 10 dependent therefrom) are therefore not rendered obvious by the combination of cited references. Moreover, there would have been no motivation to combine the cited references nor an expectation of success (see above under Rejections Under 35 U.S.C. § 103(a) (Obviousness) (2)).

In light of the foregoing, applicants respectfully request that Examiner withdraw the rejection.

Claim Objections

At page 7 of the Office Action, claims 6 and 7 were objected to as dependent on a rejected base claim.

Claims 6 and 7 depend from independent claim 1. Applicants respectfully submit that in light of the foregoing remarks, claim 1 is not rendered obvious by any of the cited references and request that the Examiner withdraw the objection to claims 6 and 7.

CONCLUSION

For the reasons set forth above, applicants submit that all grounds for rejection and objection have been overcome and that all of the pending claims are not in condition for allowance, which action is requested.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at the phone number provided below.

The fees for the Petition for a three (3)-month Extension of Time are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10592-022002.

Respectfully submitted,

Date: _____

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